1633

PATENT
Customer Number 22,852
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IN THE UNITED STATES PATENT AND TRADEMARK OFFICE

In re Application of:

DELEERSNIJDER *et al.*

Application No.: 10/030,549

§ 371 Filing Date: January 11, 2002

International Filing Date: July 17, 2000

For: HUMAN G-PROTEIN COUPLED RECEPTOR

Group Art Unit: Not yet assigned

Examiner: Not yet assigned

Commissioner for Patents
Washington, DC 20231

Sir:

PETITION TO MAKE SPECIAL
UNDER M.P.E.P. § 708.02(VIII)

Applicants petition the Commissioner of Patents and Trademarks under 37 C.F.R. § 1.102 and M.P.E.P. § 708.02(VIII) to make this application special and receive accelerated examination. In accordance with M.P.E.P. § 708.02(VIII), Applicants are enclosing a check for $130.00 to cover the fee for this Petition as set forth in 37 C.F.R. § 1.17(h). If any additional fee is required in connection with the filing of this Petition, please charge that fee to our Deposit Account No. 06-0916.

In accordance with M.P.E.P. § 708.02(VIII), all claims presented for examination are directed to a single invention. If the Patent Office determines that all of the claims are not obviously directed to a single invention, Applicants will make, without traverse, an election of claims for prosecution in this case.

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I. Preexamination Search

In accordance with M.P.E.P. § 708.02(VIII), a preexamination search was conducted in connection with a polynucleotide comprising a nucleotide sequence encoding the IGS1 polypeptide. The results of the preexamination search were provided in the International Search Report dated December 22, 2000 provided for PCT/EP00/06878. According to the International Search Report, the subject matter of the claimed invention was classified according to the International Patent Classification (IPC) as C07K 14/72, C12N 15/81, C12N 15/85, C12P 21/00, C07K 16/28, A61K 38/17, and A61K 48/00. The international search authority conducted searches on the following electronic databases: EPO-Internal, WIP Data, PAJ, STRAND, and BIOSOS.

The following electronic database "hits", scientific journal references, and published applications located by the search were determined to be representative of the art most closely related to the subject matter of the pending claims:

(A) Birren, B., *et al.* (1999) "Human clone RP11-14N15" EMBL Sequence Database Accession No: AC016468;

(B) Pavitt, R., *et al.* (2000) "Human clone RP13-13L21" EMBL Sequence Database Accession No: AL356783;

(C) Martin, F. *et al.* (1999) "The nuclear rDNA intergenic spacer of the ectomycorrhizal basidiomycete *Laccaria bicolor*: Structural analysis and allelic polymorphism," Microbiology, vol. 145, pp. 1605-1611;

(D) McKee, K.K. *et al.* (1997) "Cloning and characterization of two human G protein-coupled receptor genes (GRP38 and GRP39) related to the growth hormone

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secretagogue and neurotensin receptors," Genomics, vol. 46, pp. 426-434;

(E) Wilkie, T. *et al.* (1991) "Cloning multigene families with degenerate PCR primers," Methods: A Companion to Methods in Enzymology, vol. 2, pp. 32-41;

(F) EP 0 875 568 A1 (1998) to Bergsma, D., *et al.*;

(G) WO 96/05225 (1996) to Soppet, D., *et al.*;

(H) WO 98/20040 (1998) to Au-Young, J., *et al.*

A copy of each of the foregoing journal references and published patent applications was provided with Information Disclosure Statements and Forms PTO-1449 filed April 26, 2002 and June 14, 2002. The identification of a document in this Petition should not be construed as an admission that any document is prior art to the claims of the present application.

II. Independent Claims of the Present Invention

Claims 1, 6, 13, and 24 are independent claims and are copied below:

1. An isolated polynucleotide comprising a nucleotide sequence selected from the group consisting of :

a) a nucleotide sequence encoding the IGS1 polypeptide according to SEQ ID NO:2;

b) a nucleotide sequence encoding the polypeptide encoded by the DNA insert contained in the deposit no. CBS 102049 at the Centraalbureau voor Schimmelcultures at Baarn the Netherlands, in particular a nucleotide sequence corresponding to SEQ ID NO:1;

c) a nucleotide sequence having at least 80% (preferably at least 90%)

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sequence identity over its entire length to the nucleotide sequence of (a) or (b);

d) a nucleotide sequence which is complimentary to the nucleotide sequence of (a) or (b) or (c).

6. A DNA or RNA molecule comprising an expression system, wherein said expression system is capable of producing an IGS1 polypeptide comprising an amino acid sequence, which has at least 80% identity with the polypeptide of SEQ ID NO:2 when said expression system is present in a compatible host cell.

13. An IGS1 polypeptide comprising an amino acid sequence which is at least 80% identical to the amino acid sequence of SEQ ID NO:2 over its entire length.

24. A method of creating a genetically modified non-human animal comprising the steps of

a) ligating the coding portion of a polynucleotide consisting essentially of a nucleic acid sequence encoding a protein having the amino acid sequence SEQ ID NO:2 or a biologically active fragment thereof to a regulatory sequence which is capable of driving high level gene expression or expression in a cell type in which the gene is not normally expressed in said animal; or

b) engineering the coding portion of a polynucleotide consisting essentially of a nucleic acid sequence encoding a protein having the amino acid sequence SEQ ID NO:2 or a biologically active fragment thereof and reintroducing said sequence in the genome of said animal in such a way

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that the endogenous gene alleles encoding a protein having the amino acid sequence SEQ ID NO:2 or a biologically active fragment are fully or partially inactivated.

III. Detailed Description of the Listed Documents

Applicants' claimed invention is patentable over all of the documents listed in the preexamination search. Specifically, none of the documents listed render unpatentable the embodiments of the invention, including an isolated polynucleotide encoding the amino acid sequence of the G-protein coupled receptor IGS1 according to SEQ ID NO:2, the deposited polynucleotide of SEQ ID NO:1, a nucleotide having at least 80% sequence identity to either of these sequences, or a nucleotide complementary to these sequences, as claimed by Applicants. The claimed invention of an expression system for the expression of an IGS1 polypeptide or a polypeptide at least 80% identical to the polypeptide of SEQ ID NO:2 is not rendered unpatentable by any of these documents. Additionally, the invention of an IGS1 polypeptide of an amino acid sequence at least 80% identical to the amino acid sequence of SEQ ID NO:2 is not rendered unpatentable by the cited documents. Finally, the invention of a method of creating a genetically modified non-human animal engineered to express the IGS1 polypeptide, or inhibit expression of the amino acid sequence of SEQ ID NO:2 is not rendered unpatentable by the cited documents.

Applicants' specific comments concerning the listed documents are set forth below.

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A. Birren, B., *et al.* (1999) "Human clone RP11-14N15" EMBL Sequence Database Accession No: AC016468

This database deposit comprises human clone RP11-14N15, which contains 140,628 base pairs encompassing within it a sequence that is 99.8% identical in a 1587 base pair overlap to the sequence of the claimed invention.

This reference is not available as prior art because the date of the disclosure, December 1, 1999, falls after the priority date, July 15, 1999, of the instant application. Therefore, it does not render the invention unpatentable.

B. Pavitt, R., *et al.* (2000) "Human clone RP13-13L21" EMBL Sequence Database Accession No: AL356783

This database deposit comprises human clone RP13-13L21, which contains 175,465 base pairs encompassing within it a sequence that is 99.2% identical to a 1594 base pair overlap of the sequence of the claimed invention.

This reference is not available as prior art because the date of the disclosure, May 24, 2000, falls after the priority date, July 15, 1999, of the instant application. Therefore, it does not render the invention unpatentable.

C. Martin, F. *et al.* (1999) "The nuclear rDNA intergenic spacer of the ectomycorrhizal basidiomycete *Laccaria bicolor*: structural analysis and allelic polymorphism," Microbiology, vol. 145, pp. 1605-1611

As indicated in the International Search Report, Martin *et al.* is not prior art, as it was published after the priority date of the instant application, but is cited to understand the principles or theory underlying the invention. Applicants have provided confirmatory date stamps showing that the publication was available to the public after the priority date of the instant application, July 15, 1999. The date stamp on the reference obtained

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from the University of Minnesota Bio-Medical Library is July 30, 1999. *See* Exhibit 1.

Martin *et al.* discloses the sequence of the nuclear rDNA intergenic spacer (IGS) of the ectomycorrhizal basidiomycete *Laccaria bicolor*. *See, e.g.* Figures 2 and 3. Martin *et al.* does not teach or suggest a nucleotide sequence encoding the amino acid sequence of any G-protein coupled receptor, and in particular not the G-protein coupled receptor IGS1 according to SEQ ID NO:2 or the nucleotide sequence of SEQ ID NO:1. Because the sequence of the G-protein receptor provided in SEQ ID NO:1 or SEQ ID NO:2, or both, are elements of each of the independent claims to Applicants' invention, Martin *et al.* does not teach or suggest Applicants' invention and does not render it unpatentable.

D. McKee, K.K. *et al.* (1997) "Cloning and characterization of two human G protein-coupled receptor genes (GRP38 and GRP39) related to the growth hormone secretagogue and neurotensin receptors," Genomics, vol. 46, pp. 426-434

McKee *et al.* discloses the cloning and characterization of two novel G-protein coupled receptors, GPR38 and GPR39. *See* Figure 1. These genes were cloned using low-stringency hybridization with primers based on the related G-protein coupled receptor, GHS-R. *See* pp. 426-27. McKee *et al.* shows that GPR38 was expressed in stomach, thyroid, bone marrow, and brain, while GPR39 was expressed in tissues such as brain, stomach, and small intestine. *See* p. 433, col. 1 and Figure 4.

McKee *et al.* does not teach or suggest a nucleotide sequence encoding the amino acid sequence of the G-protein coupled receptor IGS1 according to SEQ ID NO:2 or the nucleotide sequence of SEQ ID NO:1. Because SEQ ID NO:1 or SEQ ID NO:2, or both, are elements of each of the independent claims to Applicants' invention, McKee

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et al. does not teach or suggest Applicants' invention and does not render it unpatentable.

E. Wilkie, T. *et al.* (1991) "Cloning multigene families with degenerate PCR primers," Methods: A Companion to Methods in Enzymology, vol. 2, pp. 32-41

Wilkie *et al.* provides general guidelines for isolating members of a multigene family using degenerate PCR. The reference discloses the steps of designing the degenerate PCR primers, preparing cDNA from the tissue of interest, PCR amplification, screening of PCR clones, and sequencing of the isolated DNA. *See* pp. 33-39. Specifically, Wilkie *et al.* discloses the cloning of fragments from 19 genes encoding members of the tyrosine kinase receptor subfamily that are expressed in male mouse germ cells. *See* p. 39 and Figure 2.

Wilkie *et al.*, though, does not teach or suggest a nucleotide sequence encoding the amino acid sequence of the G-protein coupled receptor IGS1 according to SEQ ID NO:2 or the nucleotide sequence of SEQ ID NO:1. Because SEQ ID NO:1 or SEQ ID NO:2, or both, are elements of each of the independent claims to Applicants' invention, Wilkie *et al.* does not teach or suggest Applicants' invention and does not render it unpatentable.

F. EP 0 875 568 A1 (1998) to Bergsma, D., *et al.*

In the International Search Report, EP 0 875 568 A1 is categorized as a reference defining the general state of the art, however the reference is not considered to be of particular relevance. EP 0 875 568 A1 discloses human neurotensin type 2 polypeptides, which are G-protein coupled 7-transmembrane receptors. *See* p. 2, lines

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5-8. The document further discusses vectors and host cells comprising the polynucleotides that encode the polypeptides, as well as assays, antibodies, vaccines, and pharmaceuticals related to the polypeptides. *See* pp. 9-13.

EP 0 875 568 A1, though, does not teach or suggest a nucleotide sequence encoding the amino acid sequence of the G-protein coupled receptor IGS1 according to SEQ ID NO:2 or the nucleotide sequence of SEQ ID NO:1. Because SEQ ID NO:1 or SEQ ID NO:2, or both, are elements of each of the independent claims to Applicants' invention, EP 0 875 568 A1 does not teach or suggest Applicants' invention and does not render it unpatentable.

G. WO 96/05225 (1996) to Soppet, D., *et al.*

WO 96/05225 discloses a seven-transmembrane receptor that is a human adrenergic receptor polypeptide and a nucleotide encoding the amino acid sequence of the receptor. *See* p. 4, lines 14-20 and Figure 1. In addition, procedures for producing the polypeptide using recombinant techniques and antibodies against the polypeptide are disclosed, as well as uses of the sequences to screen for agonists or antagonists of the receptor. *See* pp. 11-21 and Examples. The invention suggests the use of such agonists for treating upper respiratory conditions and such antagonists for treating hypertension. *See* pp. 21-22. The novel polynucleotides were isolated using PCR amplification using primers comprising sequences of the adrenergic receptor gene. *See* Example 1.

WO 96/05225 does not teach or suggest a nucleotide sequence encoding the amino acid sequence of the G-protein coupled receptor IGS1 according to SEQ ID NO:2

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or the nucleotide sequence of SEQ ID NO:1. Because SEQ ID NO:1 or SEQ ID NO:2, or both, are elements of each of the independent claims to Applicants' invention, WO 96/05225 does not teach or suggest Applicants' invention and does not render it unpatentable.

H. WO 98/20040 (1998) to Au-Young, J., *et al.*

WO 98/20040 discloses the nucleotide sequence, polypeptides sequence and related sequences for a novel histamine H2 receptor (H2RH), which is a seven-transmembrane receptor. *See* pp. 3-4 and 11-17. WO 98/20040 also discloses antagonists, agonists, and antibodies of the receptor and their therapeutic use, as well as genetically engineered vectors and host cells comprising the nucleic acid sequences encoding H2RH. *See* pp. 17-38.

WO 98/20040 does not teach or suggest a nucleotide sequence encoding the amino acid sequence of the G-protein coupled receptor IGS1 according to SEQ ID NO:2 or the nucleotide sequence of SEQ ID NO:1. Because SEQ ID NO:1 or SEQ ID NO:2, or both, are elements of each of the independent claims to Applicants' invention, WO 98/20040 does not teach or suggest Applicants' invention and does not render it unpatentable.

Thus, none of the references cited in the International Search Report render the claimed invention unpatentable. Each of the references is either unavailable as prior art or does not teach or suggest a nucleotide sequence encoding the amino acid sequence of the G-protein coupled receptor IGS1 according to SEQ ID NO:2 or the nucleotide sequence of SEQ ID NO:1. Without disclosure of SEQ ID NO:1 or SEQ ID NO:2 in a

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reference available as prior art, Applicants' invention is patentable.

IV. Documents Referenced in the Specification

The specification refers to documents that are grouped in the categories provided below. None of these documents teach or suggest a nucleotide sequence encoding the amino acid sequence of the G-protein coupled receptor IGS1 according to SEQ ID NO:2, or the nucleotide sequence of SEQ ID NO:1, as claimed by Applicants.

A. G-Protein Receptors and Pathways

The following documents, referenced on pages 1-3 of the specification, provide an overview of the field of G-Protein receptors and pathways. They include:

- Lefkowitz, R.J. (1991) Thrombin receptor, Variations on a theme, Nature, vol. 351, pp. 353-54 - providing a general review of the thrombin receptor;
- Kobilka, B.K., *et al.* (1987) cDNA for the human beta 2-adrenergic receptor: A protein with multiple membrane-spanning domains and encoded by a gene whose chromosomal location is shared with that of the receptor for platelet-derived growth factor, Proc. Natl. Acad. Sci. U.S.A. vol., 84, pp. 46-50 - disclosing isolation and characterization of a cDNA encoding the human beta 2-adrenergic receptor;
- Kobilka, B.K., *et al.* (1987) Cloning, sequencing, and expression of the gene coding for the human platelet alpha 2-adrenergic receptor, Science, vol. 238, pp. 650-56 - describing cloning and characterization of the human platelet alpha 2-adrenergic receptor and showing that the gene has homology with human beta 1

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and beta 2-andrenergic receptors;

- Bunzow, J.R., *et al.* (1988) Cloning and expression of a rat D2 dopamine receptor cDNA, Nature, vol. 336, pp. 783-787 - using the expected nucleotide sequence similarities among members of the dopaminergic receptors to isolate a novel D2 dopamine receptor gene from rat;
- Simon, M.I., *et al.* (1991) Diversity of G proteins in signal transduction, Science, vol. 252, pp. 802-08 - providing a general overview of G protein signalling and discussing a large family of G proteins expressed in all eukaryotic cells;
- McLatchie, L.M., *et al.* (1998) RAMPs regulate the transport and ligand specificity of the calcitonin-receptor-like receptor, Nature, vol. 393, pp. 333-39 - describing a calcitonin-receptor-like receptor that can either function as a calcitonin-gene-related peptide or as an adrenomedullin receptor;
- Johnson, G.L. and Dhanasekaran, N. (1989) The G-protein family and their interaction with receptors, Endocr. Rev., vol. 10, pp. 317-31 - providing general reviews of the art; and
- Drews, J. (1996) Genomic sciences and the medicine of tomorrow, Nat. Biotechnol., vol. 14, pp. 1516-1518 - providing general reviews of the art.

B. Polypeptide Modifications

The following documents, referenced on page 10 of the specification, provide methods for chemical modifications that can be made to polypeptides, such as ubiquitination, attachment of a lipid, crosslinking, and phosphorylation. The references include:

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- Proteins - Structure and Molecular Properties, 2nd Ed., Creighton, T.E., Ed., W.H. Freeman and Co., New York, pgs. 1-12 (1993);
- Wold, F., Posttranslational Protein Modifications: Perspectives and Prospects, *in* Posttranslational Covalent Modification of Proteins, B.C. Johnson, Ed., Academic Press, New York, (1983);
- Seifter, S. and Englard, S. (1990) Analysis for protein modifications and nonprotein cofactors, Methods Enzymol., vol. 182, pp. 626-46; and
- Rattan, S.I., *et al.* (1992) Protein synthesis, posttranslational modifications, and aging, Ann. N.Y. Acad. Sci., vol. 663, pp. 48-62.

C. Identity of Polypeptide or Nucleotide Sequences

The following documents, referenced on page 11 of the specification, provide methods for determining "identity" of nucleotide or amino acid sequences. The documents include:

- Computational Molecular Biology, Lesk, Ed., Oxford University Press, New York (1988);
- Biocomputing: Informatics and Genome Projects, Smith, D.W. Ed., Academic Press, New York (1993);
- Computer Analysis of Sequence Data, Part I., Griffin, A.M. and Griffin, H.G., eds., Humana Press, New Jersey (1994);
- Sequence Analysis in Molecular Biology, von Hienje, G., Academic Press, San Diego (1987);
- Sequence Analysis Primer, Gribskov, M. and Devereux,. J. eds., M Stockton

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Press, New York (1991);

- Carillo, H. and Lipton, D (1988) SIAM, J. Applied Mathematics, vol. 48, p. 1073;
- Guide to Huge Computers, Bishop, M.J., Ed., Academic Press, San Diego (1994);
- Devereux, J. *et al.* (1984) A comprehensive set of sequence analysis programs for the VAX, Nucleic Acids Res. vol. 12, pp. 387-95; and
- Altschul, S.F., *et al.* (1990) Basic local alignment search tool, J. Mol. Biol., vol. 215, pp. 403-10.

D. Structural Analysis

Methods of determining the structural relationship of IGS1 to other proteins are provided in the following references, which do not disclose SEQ ID NO:1 or SEQ ID NO:2. Such references are found on page 15 of the specification, and include:

- Altschul, S.F. *et al.* (1997) Gapped BLAST and PSI-BLAST: A new generation of protein database search programs, Nucleic Acids Res., vol. 25, pp. 3389-402;
- Miyamoto, S. *et al.* (1997) Cloning, functional expression and tissue distribution of rabbit alpha1a-adrenoceptor, RL Life Sci., vol. 60, pp. 2069-74;
- Bruno, J.F., *et al.* (1991) Molecular cloning and sequencing of a cDNA encoding a human alpha 1A adrenergic receptor, Biochem. Biophys. Res. Comm., vol. 179, pp. 1485-90; Hofmann, K.; and
- Stoffel, W. (1993) Biol. Chem. Hoppe-Seyler, vol. 347, pp. 166.

E. Isolating and Characterizing a Protein

The specification at pages 15-18 describes general methods for preparing, and

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expressing proteins. The cited references include:

- Libert, F. *et al.* (1989) Selective amplification and cloning of four new members of the G protein-coupled receptor family, Science, vol. 244, pp. 569-72;
- Gentz, R., *et al.* (1989) Bioassay for trans-activation using purified human immunodeficiency virus tat-encoded protein: trans-activation requires mRNA synthesis, Proc. Natl. Acad. Sci. U.S.A., vol. 86, pp. 821-24;
- Davis, *et al.*, Basic Methods in Molecular Biology, Appleton & Lange, Norwalk, CT (1986); and
- Sambrook, *et al.*, Molecular Cloning: A Laboratory Manual, 2nd Ed., Cold Spring Harbor Laboratory Press, Cold Spring Harbor, N. Y. (1989).

F. Diagnostic Assays

References listed in the specification at page 19 describe methods for designing and producing diagnostic tests to detect a protein or DNA. Such methods could be used to detect a susceptibility to a disease or diagnose a disease state. These references do not teach or suggest specific assays for diagnosing or detecting the IGS1 polypeptide or the gene that encodes it. These references include:

- Myers R.M., *et al.* (1985) Detection of single base substitutions by ribonuclease cleavage at mismatches in RNA:DNA duplexes, Science, vol. 230, pp. 1242-46;
- Cotton, *et al.* Reactivity of cytosine and thymine in single-base-pair mismatches with hydroxylamine and osmium tetroxide and its application to the study of mutations (1985) Proc. Natl. Acad. Sci. U.S.A. vol. 85, pp. 4397-401; and
- Chee, M., *et al.* (1996) Accessing genetic information with high-density DNA

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arrays, Science, vol. 274, pp. 610-614.

G. Chromosome Assays

A reference on page 21 of the specification provides information on correlating mapping genetic sequences to a positions on chromosomes, though not specifically for the sequence of SEQ ID NO:2. This reference is McKusick, V. Mendelian Inheritance in Man, available on the Johns Hopkins University Welch Medical Library intranet site at <http://www.ncbi.nlm.nih.gov/entrez/query.fcgi?db+OMIM>.

H. Antibodies

The references cited on pages 21-22 of the specification provide general guidelines for producing antibodies directed against a specific polypeptide. They do not, however, specifically teach or suggest raising antibodies against the IGS1 polypeptide. These references include:

- Kohler, G and Milstein, C. (1975) Continuous cultures of fused cells secreting antibody of predefined specificity, Nature, vol. 256, pp. 495-97;
- Kozbor, D. and Roder, J.C. (1983) The production of monoclonal antibodies from human lymphocytes, Immunology Today, vol. 4, pp. 72-79; and
- Reisfeld, R.A. and Sell, S. (1985) Monoclonal Antibodies and Cancer Therapy, Alan R. Liss, Inc., New York.

I. Transgenic Animals

Transgenic animals could be made that express an increased level of IGS1, a decreased level of IGS1, or an altered IGS1 protein. General methods for producing transgenes and animals are provided in references cited in the specification at pages

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23-24. None of these references teach or suggest making transgenic animals in which the expression of IGS1 is altered. These references include:

- Hoppe, P.C. and Wagner, T.E. U. S. Patent No. 4,873,191 (1989);
- van der Putten, H. *et al.* (1985) Efficient insertion of genes into the mouse germ line via retroviral vectors, Proc. Natl. Acad. Sci. U.S.A., vol. 82, pp. 6148-52;
- Thompson, S, *et al.* (1989) Germ line transmission and expression of a corrected HPRT gene produced by gene targeting in embryonic stem cells, Cell, vol. 56, pp. 313-21;
- Lo, (1983) Transformation by iontophoretic microinjection of DNA: Multiple integrations without tandem inserts, Mol. Cell. Biol., vol. 3, pp. 1803-14;
- Lavitrano, M., *et al.* (1989) Sperm cells as vectors for introducing foreign DNA into eggs: Genetic transformation of mice, Cell, vol. 57, pp. 717-23;
- Gordon, J.W. (1989) Transgenic animals, Int. Rev. Cytol., vol. 115, pp. 171-229;
- Jakobovits, A. (1994) YAC vectors: Humanizing the mouse genome, Curr. Biol., vol. 4, pp. 761-63;
- Lasko, M., *et al.* (1992) Targeted oncogene activation by site-specific recombination in transgenic mice, Proc. Natl. Acad. Sci. U.S.A., vol. 89, pp. 6232-36; and
- Gu, H, *et al.* (1994) Deletion of a DNA polymerase beta gene segment in T cells using cell type-specific gene targeting, Science, vol. 256, pp. 103-06.

J. Detecting Agonists or Antagonists

King, K., U.S. Patent No. 5,842,835 (1996), provides methods for detecting

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agonists or antagonists of a polypeptide using yeast-based technology, as cited on page 27 of the specification. The reference does not address IGS1.

K. Prophylactic and Therapeutic Methods

The following references, cited on page 29 of the specification, reveal methods for producing and using polypeptides and genes expressing the polypeptides for prophylactic or therapeutic use. The references do not teach or suggest prophylactic or therapeutic methods involving the IGS1 receptor. These references include:

- O'Connor, J. Oligodeoxynucleotides as Antisense Inhibitors of Gene Expression, CRC Press, Boca Raton, FL (1988);
- Lee, J.S., *et al.* (1979) Complexes formed by $(pyrimidine)_n.(purine)_n$ DNAs on lowering the pH are three stranded, Nucleic Acid Res., vol. 6, pp. 3073-91;
- Cooney, M., *et al.* (1988) Site-specific oligonucleotide binding represses transcription of the human c-myc gene *in vitro*, Science, vol. 241, pp. 456-59;
- Beal, P.A. and Dervan, P.B. (1991) Second structural motif for recognition of DNA by oligonucleotide-directed triple-helix formation, Science, vol. 251, pp. 1360-63; and
- Lisman, N., (1996) Hammerhead ribozyme engineering, Curr. Opin. Struct. Biol., vol. 6, pp. 527-533; and
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L. ESTs

On page 35 of the specification, two ESTs associated with the ISG1 contig are described. These ESTs, which are present in Genbank under the accession numbers AA318717 and AI672141, do not include the sequences of the IGS1 open reading frame, including SEQ ID NO:1 or SEQ ID NO:2, as indicated in the specification. Therefore, these references do not teach or suggest the claimed invention.

V. Conclusion

Applicants submit that the requirements of M.P.E.P. § 708.02(VIII) have been met. In addition, the pending claims are allowable over the above references considered either individually or in any reasonable combination.

Accordingly, Applicants respectfully request that the Patent Office grant this Petition and allow the claims of this application.

Respectfully submitted,

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